

Force-induced unzipping of DNA with long-range correlated sequence

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We consider force-induced unzipping transition for a heterogeneous DNA model with a long-range correlated base-sequence. It is shown that as compared to the uncorrelated situation, long-range correlations smear the unzipping phase-transition, change its universality class and lead to non-self-averaging: the averaged behavior strongly differs from the typical ones. Several basic scenarios for this typical behavior are revealed and explained. The results can be relevant for explaining the biological purpose of long-range correlations in DNA.

Introduction. Structural transformations of DNA under changing of external conditions are of primary importance for molecular biology and biophysics¹. They take place in transcription of genetic information from DNA and in duplication of DNA during cell division¹. The common physical scenario of both these processes is unwinding of the double-stranded structure of DNA under influence of external forces. Whereas theoretical and experimental studies of thermal denaturation (melting) of DNA have a long history, force-induced unzipping has been actively investigated only relatively recently^{2,3,4,5}; for a concise review and more references see⁴. The research in this field is motivated by the new generation of micromanipulation experiments⁵. For the theoretical understanding of the subject both homo and heteropolymer models of DNA were studied^{2,3,4}.

The main purpose of the present letter is to make the next step towards real DNAs and to analyze force-induced unzipping for a DNA-model, where the correlation structure of the base-sequence is taken into account. Indeed, one of the main differences between DNA and other biopolymers⁶ is that the base-sequence of the former displays long-range correlations (1/f-noise spectrum)^{7,8,9}; for a review see¹¹. Recall that the base-sequence of a DNA molecule consists of purines (A and G) and pyrimidines (C and T). They constitute the genetic code carried by DNA. Initial studies reported long-range correlations for non-coding regions of DNA, while more recent results show that certain types of them can also exist in coding regions¹⁰. Moreover, systematic changes were found in the structure of correlations depending on the evolutionary category of the DNA carrier^{8,9}. In spite of ubiquity of long-range correlations in DNA-structures, their biological reason remains basically unexplored.

We will show below that long-range correlations present in the base-sequence of DNA make its behavior under the unzipping external force essentially non-self-averaging: there are several widely different scenarios of behavior which specifically depend on the concrete structure of the base-sequence and are not reproduced by the averaged behavior. This is in contrast to DNAs with short-range correlated base-sequence whose behavior in the vicinity of the unzipping transition is perfectly self-averaging: almost every molecule behaves (in the ther-

modynamic limit) similar to the average.

The model we will work with takes into account the most minimal amount of physical ingredients needed to describe force-induced unzipping. *i)* a DNA molecule is lying along the x -axis between the points $x = a$ and $x = L$. *ii)* only inter-strand (hydrogen) bonds of the molecule are considered; they are located at points x_i , $a < x_i < L$, $i = 1, \dots, M$. Any bond can be in one of two states: bound or broken. We choose the overall energy scale in such a way that the latter case contributes to the Hamiltonian a binding energy $\phi(x_i)$, whereas the former case brings nothing. Different types of bonds do have different binding energies, so $\phi(x_i)$ is a random quantity with an average $\langle \phi \rangle$: $\phi(x_i) = \langle \phi \rangle + \eta(x_i)$. *iii)* a force is acting on the left end $x = a$ of the molecule pulling apart the two strands. Thus, if a bond x_i is broken, all the bonds x_j with $j < i$ are broken as well. Each broken bond brings additionally to the Hamiltonian a term $-\mathcal{F}$, where \mathcal{F} is proportional to the acting force. *iv)* summarizing all of these, one comes to the Hamiltonian $H(x) = -\mathcal{F}x + \sum_{i=1}^x \phi(x_i) = (\langle \phi \rangle - \mathcal{F})x + \sum_{i=1}^x \eta(x_i)$, where x is the number of broken bonds. In the thermodynamical limit, where L and M are large, one applies the continuum description with x being a real number, $a < x < L$, and ends up with the following Hamiltonian and partition function:

$$H(x) = f(x - a) + \int_a^x ds \eta(s), \quad Z = \int_a^L dx e^{-\beta H(x)}, \quad (1)$$

where $f = \bar{\phi} - \mathcal{F}$ and $\beta = 1/T$ is the inverse temperature ($k_B = 1$). It remains to specify the properties of the noise η . Strictly speaking, it can take values corresponding to inter-strand bonds AT and GC. However, within the adopted description we assume it is a gaussian stationary process with an autocorrelation function $K(t - t') = \langle \eta(t)\eta(t') \rangle$ to be specified later on. The model given by (1) and by $K(t) \propto \delta(t)$ (white noise) is well-known, and was used to describe interfaces, random walks in a disordered media, and aspects of population dynamics¹². It was recently applied for the unzipping transition in DNA³.

Reduction to a stochastic differential equation. In Eq. (1) one fixes L , and views a as a parameter varying from the highest possible value L , where $Z = 0$, to the

lowest possible value which we define to be $a = 0$. The quantity $t = -a$ will thus monotonically increase and can be interpreted as a time-variable. Differentiating Z in (1) over a and changing the variable as $t = -a$, one gets:

$$\frac{dZ}{dt} = 1 - \beta f Z - \beta \eta(t) Z, \quad -L < t < 0 \quad (2)$$

where we used $\eta(t) = \eta(-t)$, as follows from the gaussian stationary property of the noise. This is a Langevin equation with a multiplicative noise. From (2) one can obtain a stochastic equation for $F = -T \ln Z$:

$$\frac{dF}{dt} + V'(F) = \eta(t), \quad V(F) = T^2 e^{\beta F} - fF. \quad (3)$$

The *order parameter* of the problem is the number of broken bonds. Along with its average and variance it is defined for $t = 0$ as

$$x = \partial_f F, \quad \bar{x} = \partial_f \langle F \rangle, \quad \overline{\Delta x^2} \equiv \overline{x^2} - \bar{x}^2 = -T \partial_f \bar{x}. \quad (4)$$

Exponentially correlated noise. As the first example we shall consider Ornstein-Uhlenbeck (OU) noise $K(t) = (D/\tau) e^{-|t|/\tau}$, where D is the intensivity, and τ is the correlation time. Although for a finite τ this noise is short-range correlated, we believe that it correctly catches the basic trends of the more general situation when changing τ from 0 to some large value. Note that the white-noise situation is recovered for $\tau \rightarrow 0$.

To handle (3) one differentiates it over t and uses the generating equation for OU process $\tau \dot{\eta} = -\eta + \sqrt{D} \xi(t)$, where $\xi(t)$ is a white gaussian noise: $\langle \xi(t) \xi(t') \rangle = 2\delta(t - t')$. Introducing $s = t/\sqrt{\tau}$ one gets¹⁴:

$$\frac{d^2 F}{ds^2} + \gamma(F) \frac{dF}{ds} = -V'(F) + \frac{\sqrt{D}}{\tau^{1/4}} \xi(s), \quad (5)$$

where $\gamma(F) = 1/\sqrt{\tau} + \sqrt{\tau} V''(F)$. Recall that Eq. (5) has the same form as a Langevin equation for a particle with unit mass in the potential $V(F)$ and subjected to a white noise and a F -dependent friction with a coefficient $\gamma(F)$. $V(F)$ is confining only for $f > 0$: $V(F) \rightarrow \infty$ for $F \rightarrow \pm\infty$. As well-known¹³, for sufficiently long times one can neglect the inertial term $d^2 F/ds^2$, provided that at least one of the following conditions are satisfied: (i) the dependence on F in $\gamma(F)$ is weak; (ii) $\gamma(F)$ is sufficiently large. If $V''(F)$ is of order one, then the second condition is satisfied both for large and small τ ¹⁴. If $V''(F)$ is small then the first condition is satisfied. After neglect of the inertial term in (5), the remainder is an ordinary white-noise Langevin equation, and, by means of standard methods¹³, can be transferred to a Fokker-Planck equation for the distribution function $P(F, s) = \langle \delta(F - F[s]) \rangle$, where $F[s]$ is a particular, noise-dependent solution of (5).

$$\frac{\partial P}{\partial s} - \frac{\partial}{\partial F} \frac{V'(F)}{\gamma(F)} P(F) = \frac{D}{\sqrt{\tau}} \frac{\partial}{\partial F} \frac{1}{\gamma(F)} \frac{\partial}{\partial F} \frac{P(F)}{\gamma(F)}. \quad (6)$$

For large times (lengths), i.e. for $L \gg 1$ and $t \propto s \rightarrow 0$, any solution of (6) tends to the stationary distribution

(see e.g.¹³ for a general proof) obtained from (6) by putting $\partial_s P = 0$:

$$P_{st}(F) = \mathcal{N} \gamma(F) \exp \left[-\frac{\tau}{2D} [V'(F)]^2 - \frac{1}{D} V(F) \right], \quad (7)$$

where \mathcal{N} is the normalization factor. The white-noise, $\tau \rightarrow 0$, limit of $P_{st}(F)$ was obtained in^{3,12}.

The critical domain of the model corresponds to $f \rightarrow +0$, where the average energy cost for breaking a hydrogen bond tends to zero. Our aim is to compare in this domain the behavior of \bar{x} for a finite τ with that of $\tau = 0$ (white-noise) as to determine the effect of the noise-correlation. Recall from¹² that for $\tau = 0$ a simple formula exists: $\bar{x} = T^2 \psi'(\mu)$, where $\mu = Tf/D$ and $\psi'(\mu) = d^2 [\ln \Gamma(\mu)]/d\mu^2$. Thus for $f \propto \mu \rightarrow 0$, \bar{x} becomes large³: $\bar{x} = D/f^2$. One can explain this by noting that for $f \rightarrow 0$ the potential $V(F)$ in (3) ceases to be confining, and the particle escapes to infinity. Note that here the random quantity x is concentrated around its average: $\overline{\Delta x^2}/\bar{x}^2 \propto f \rightarrow 0$. Thus, in the present context a given DNA molecule with a typical base-sequence does not have individuality: its behavior coincides with the averaged one.

$P_{st}(F)$ and \bar{x} can be expressed via Kummer functions and then easily studied numerically. Fig. (1) shows that although the behavior of \bar{x} for very small f does not depend much on τ , such a dependence does exist for moderately small values of f : finite τ 's smear the small- f singularity and thus increase the stability of the DNA molecule, since larger external forces \mathcal{F} are demanded to achieve the same amount of broken bonds.

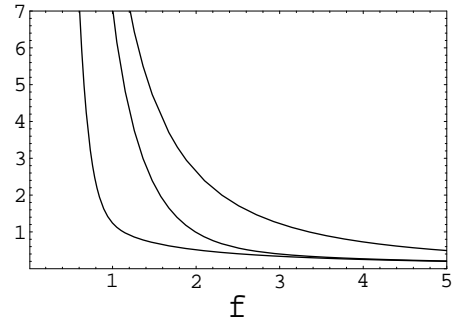


FIG. 1: The order parameter \bar{x} versus f for Ornstein-Uhlenbeck noise with $D = 10$, $T = 1$. From right to left: $\tau = 0$, $\tau = 10$, $\tau = 100$.

Long-range correlations will be modelled via a stationary gaussian noise with an autocorrelation function⁹:

$$K(t) \equiv \langle \eta(t) \eta(0) \rangle = \sigma |t|^{-\alpha}, \quad (8)$$

where $0 < \alpha < 1$ is the exponent characterizing the long-range correlation, and where σ is the intensivity. Although the real noise distributions in DNA can be much more complicated^{10,11}, (8) is certainly the minimal model of noise which allows to study long-range correlations.

To start with, let us consider a case with $\alpha = 0$, which does not have a direct physical interest and does not allow

the strict thermodynamical limit, but, as seen later, it is still able to provide a relevant insight. The noise is now completely frozen: $\eta(s)$ in (1) does not depend on s , and due to this the problem is easily solved from (1):

$$\frac{\bar{x}}{L} = \langle g(\eta) \rangle, \quad g(\eta) \equiv \frac{T}{L(f+\eta)} - \frac{1}{e^{\beta L(f+\eta)} - 1}, \quad (9)$$

where $\langle \dots \rangle$ is taken over the zero-average gaussian random quantity η whose dispersion is σ . If βL is large, $g(\eta)$ behaves as the step-function, $g(\eta) \simeq \theta(-\eta - f)$: for any single realization of the noise there is a sharp phase transition with a jump at the realization-dependent point $f = -\eta$ (non-self-averaging). In contrast, due to the integration over η in (9), the behavior of \bar{x} is smooth, and there remains only a crossover between small \bar{x}/L for a large f and $\bar{x} = L/2$ for $f = 0$: the sharp transition disappears.

We return to Eq. (2) with the noise $\eta(t)$ characterized by (8). Our aim is to obtain a Fokker-Planck equation for the probability density $P(Z, t) = \langle \delta(Z - Z[t]) \rangle$, where $Z[t]$ is a noise-dependent solution of (2). Differentiating $P(Z, t)$ over t and using (2), one gets:

$$\frac{\partial P}{\partial t} + \frac{\partial}{\partial Z} [(1 - \beta f Z) P] = \beta \frac{\partial}{\partial Z} Z \langle \eta(t) \delta(Z - Z[t]) \rangle. \quad (10)$$

To handle the last term, one uses the fact that the noise is gaussian and applies Novikov's theorem¹⁵, to obtain

$$\begin{aligned} \langle \eta(t) \delta(Z - Z[t]) \rangle &= \int_{-L}^t ds K(t-s) \left\langle \frac{\delta}{\delta \eta(s)} \delta(Z - Z[t]) \right\rangle \\ &= -\frac{\partial}{\partial Z} \int_{-L}^t ds K(t-s) \left\langle \delta(Z - Z[t]) \frac{\delta Z[t]}{\delta \eta(s)} \right\rangle, \end{aligned} \quad (11)$$

where $\delta/\delta \eta(s)$ is the variational derivative, the equation for which is obtained from (2). Solving this equation and using

$$Z[s] = \exp \left[\int_t^s du \left(\frac{1}{Z[u]} - \beta f - \beta \eta(u) \right) \right] Z[t], \quad (12)$$

also obtained from (2), one finally gets

$$\begin{aligned} \langle \eta(t) \delta(Z - Z[t]) \rangle &= \frac{\partial}{\partial Z} Z \int_{-L}^t ds K(t-s) \times \\ &\left\langle \delta(Z - Z[t]) \exp \left[- \int_s^t \frac{du}{Z[u]} \right] \right\rangle. \end{aligned} \quad (13)$$

Eqs. (10, 13) are exact, but since now approximations have to be applied to get a closed equation for $P(Z, t)$. Note from (2, 3) the following relation valid in the stationary state: $\langle 1/Z \rangle = \beta f$. For $f \rightarrow +0$ this relation can be satisfied only if the corresponding stationary distribution tends to become non-normalizable due to its large- Z behavior. Thus, we can search for this distribution assuming that the characteristic values of Z are large. For

this one takes the thermodynamical limit $L \gg 1$, $t \rightarrow 0$, makes partial integration in the RHS of (13), uses (2), and gets for $\phi(Z, s) \equiv \int_0^s du/Z[\eta, u]$ ($\beta f \ll 1$):

$$\phi(Z, s) = \frac{s}{Z[\eta, s]} - \beta \int_0^s \frac{du u \eta(u)}{Z[\eta, u]} + \int_0^s \frac{du u}{Z^2[\eta, u]}. \quad (14)$$

Now the last term can be neglected due to the above large- Z property. Assuming additionally that the magnitude of the noise $\eta(t)$ is small, one can estimate the second term in the RHS as being at least of order $\mathcal{O}(1/Z^2)$ and neglect it as well. For the first term in the RHS of (14) one uses (12) to express $Z(s)$ by $Z(0)$ which due to the delta-function in (13) can be substituted by Z . The noise in the resulting equation for ϕ is again neglected, and then ϕ is determined from:

$$Z \phi(Z, s) = s e^{-\phi(Z, s) + \beta f s}. \quad (15)$$

Thus the stationary distribution reads

$$P_{\text{st}}(Z) = \frac{\mathcal{N}}{Z \mathcal{D}(Z)} \exp \left[\int^Z \frac{du}{u \mathcal{D}(u)} \left(\frac{T}{u} - f \right) \right], \quad (16)$$

where \mathcal{N} is the normalization (the lower limit of integration is not specified, since it can be absorbed to \mathcal{N}), and where

$$\mathcal{D}(Z) = \int_0^\infty ds K(s) e^{\phi(Z, -s)}. \quad (17)$$

To study the critical behavior of \bar{x} , one needs two asymptotic regimes found from (15, 17): $\mathcal{D}(Z) \propto Z^{1-\alpha} e^{\beta f(1-\alpha)Z}$ for $\beta f Z \ll 1$, while $\mathcal{D}(Z)$ is constant for $\beta f Z \gg 1$. Substituting these into (16) and selecting the most divergent terms, one gets:

$$\bar{x} \simeq \frac{\Gamma(\alpha)}{\tilde{\sigma}(\beta f)^\alpha} \ln \frac{1}{\beta f}, \quad \kappa \equiv \frac{\overline{\Delta x^2}}{\bar{x}^2} \simeq \frac{\tilde{\sigma}(\beta f)^{\alpha-1}}{\Gamma(\alpha) \ln \frac{1}{\beta f}}, \quad (18)$$

where $\tilde{\sigma} = \sigma^{(1-\alpha)/(2-\alpha)}$. Due to the above weak-noise assumption, (18) represents the leading term of the small- $\tilde{\sigma}$ expansion. It is seen that in contrast to the white-noise situation the behavior of \bar{x} is smeared, and that x is strongly non-self-averaging quantity: $\kappa \gg 1$ for $\beta f \ll 1$ (recall^{3,12} that in the white-noise case: $\bar{x} \simeq f^{-2}$ and thus $\kappa \simeq f^{-1} \rightarrow 0$ for $f \rightarrow 0$). Both these results are contrasting to qualitative predictions made in³: $\bar{x} \simeq f^{-2/\alpha}$, $\kappa \simeq f^{-1+2/\alpha} \rightarrow 0$, which means that the small- f singularity is stronger and x is even more self-averaging than in the white-noise case. We think that this discrepancy is due to inapplicability of the reasonings made in³ for finite temperatures.

Typical scenarios of unzipping. The above results on non-self-averaging indicate that $\bar{x}(f)$ is not directly relevant for experiments which are carried out on single DNA molecules: one should study different realizations of the noise and identify typical, i.e. frequently met, scenarios of behavior. Results of extensive numerical investigation

of this problem will be reported elsewhere¹⁷. Here we discuss some representative examples. By means of direct numerical enumeration of $L = 10^4$ discrete base-pairs we studied the behavior of the (unaveraged) order parameter x as a function of f . The long-range correlated gaussian discrete-time stochastic process was generated following to optimized recipes proposed in¹⁶. As compared to (8), the noise was regularized at short distances due to obvious numerical reasons. We focus on the thermodynamical domain where f is not very small, and thus comparison with the theory is possible. In the (regularized) white noise case the simulations are in perfect agreement with the theory: x is self-averaged and $\bar{x} \propto f^{-2}$ is reproduced. In contrast to that a strong non-self-averaging is present for the long-range correlated noise. Moreover, we found several radically different scenarios of the typical behavior. Two extremal ones among them are presented in Figs. 2, 3. The first one is present in nearly 12% of all realizations and is demonstrated by Fig. 2. It is characterized by very smooth, non-critical behavior of $x(f)$ for $f \geq 0$. Fig. 3 presents a strictly different situation: $x(f)$ increase by several jumps followed by very flat regions. $x(0)$ is either equal to its maximal possible value L or close to it. This phase-transition scenario is met in nearly 45% of all realizations. Other typical realizations are intermediate between these two extremes. Our discussion of the frozen noise made after (9) allows to explain this jump-plateau structure. A sizeable portion of long-range correlated noise realizations can be qualitatively visualized as several pieces of the frozen noise with different η put next to each other. Now recall from (9) that every sufficiently long piece of that type has a single first order phase transition with a jump proportional to its length.

In conclusion, we have shown that long-range correlations in the base-sequence of a model DNA drastically influence its unzipping under external force: *i*) the behavior of the average order parameter in the critical regime is smeared; *ii*) the situation is essentially non-self-averaging: there are several scenarios of typical unzip-

ping which do not coincide with the averaged behavior; *iii*) long-range correlations increase the adaptability of the molecule, since in some typical scenarios it becomes more stable with respect to the force, while in others the

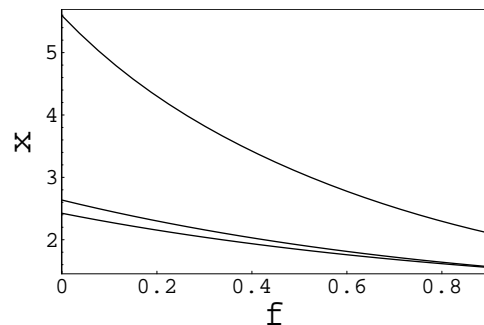


FIG. 2: $x(f)$ for three realizations of the noise within one class of typicality. $T = \sigma = 1$, $L = 10^4$ and $\alpha = 0.5$.

unzipping phase transition is amplified. What scenario will be selected depends on the detailed structure of the base-sequence. Some of the above tendencies, e.g. the smearing, are seen already for a short-range correlated base-sequence. We hope that these results will contribute into understanding of the role and the purpose of long-range correlations in DNA.

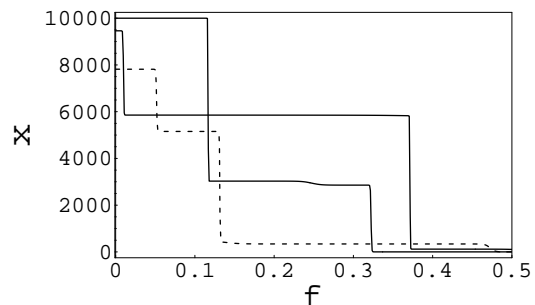


FIG. 3: $x(f)$ for three realizations of the noise within another class of typicality. $T = \sigma = 1$, $L = 10^4$ and $\alpha = 0.5$.

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